REMARKS

The Notice concerns the alleged non-compliance of claim 36 in the Amendment to the Claims submitted on October 22, 2009. Specifically, the Examiner requires Applicants to clarify the status of claim 36 as either "Previously presented" or "Cancelled." Applicants hereby change the identifier of claim 36 from "Withdrawn" to "Cancelled" and remove the text of the claim. As evidenced in the Remarks submitted on October 22, 2009, solely to expedite the prosecution of the application, claim 36 is cancelled without prejudice to possible future prosecution. Although the submission of the above corrected listing of the claims would be fully responsive to the Notice, for clarity, Applicants hereby also recite the Remarks submitted on October 22, 2009 by modifying the relevant parts of the text related to the status of claim 36. Therefore, no new matter is introduced in the above amendment, and no new argument is presented in the following remarks.

STATUS OF THE CLAIMS

Claims 22-36 were pending in this application. Claims 29-34 were withdrawn from consideration pursuant to the restriction requirement. Claims 1-21 were cancelled. Claims 22-24, 26-28 and 35 are objected to for informalities. Claims 22-28, 35 and 36 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite and under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Claim 36 is also rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Zimmermann et al. (*Molecular Human Reproduction*, 2003, Vol. 9, 81-89). Claim 36 is hereby cancelled without prejudice to possible future prosecution. Claims 22-24, 26-28 and 35 are amended. Upon entry of this amendment, claims 22-35 are pending in this application, but claims 29-34 are withdrawn from further consideration.

Reconsideration of the Office Action is respectfully requested in view of the above amendments and the following remarks.

AMENDMENT OF THE CLAIMS

Claim 22 is amended by deleting the term "ehCG" to clarify that the method relates to the determination of the eβhCG subunit and by replacing the term "and" with the term "and/or" to

clarify that it is not in any case necessary to determine endometrial and non trophoblastic hCG variants. No new matter is introduced.

Claim 22 is also amended by changing the preamble from "A method for determining defined states or modifications in the mucous membrane of the uterus or in the epithelium of other organs" to "A method for determining the receptivity of the endometrium and/or optimal implantation conditions in the uterus and/or presence of an undisturbed pregnancy." Support is found throughout the specification, for example, in the translation of the application as filed (WO-A2 2004/109292), on page 5, third paragraph.

Claim 22 is also amended by deletion of the clause "wherein a reduction of expression of endometrial chorionic gonadotropin (eßhCG/ehCG) in a pregnant woman with a healthy pregnancy signals a dysfunction of the endometrium or decidua, a pregnancy disorder due to a dysfunction of the decidua and a risk of miscarriage, intra-uterine growth retardation, preeclampsia, a premature birth or, at the end of pregnancy, the onset of labor" and specifying the origin of samples in the other clauses. Support is found throughout the specification, for example, the translation of the original application (WO-A2 2004/109292), from page 8 through 17.

Claims 22 to 24, 28 and 35 are amended, according to the examiner's recommendation, by adding the SEQ ID NO.'s of the recited proteins. No new matter is introduced.

Claim 24 and 35 are amended by inserting the phrase "comprises using" before the phrase "at least one antibody" and deleting the phrase "is used," as suggested by the Examiner. No new matter is introduced.

Claims 22, 26 and 27 are amended for consistency reasons by inserting the term "human" in front of term "endometrial hCG," as suggested by the Examiner. No new matter is introduced.

Claim 26 is also amended by changing dependency from claim 22 to claim 23, thus correcting the "lack of antecedent basis" issue for trophoblastic hCG or total βhCG or total hCG. No new matter is introduced.

Claim 28 is amended so that it clearly relates to the methods of the previous claims and specifies the samples used in said method. No new is introduced.

THE INVENTION

The instant invention is drawn to, *inter alia*, a method for determining the receptivity of the endometrium and/or optimal implantation conditions in the uterus and/or presence of an undisturbed pregnancy, the method comprising the step of:

determining specifically a concentration of at least one of human endometrial chorionic gonadotropin (eßhCG; SEQ ID NO. 10) and/or non-trophoblastic hCG (hCG type I, ß6 and ß7; SEQ ID NO. 9) in a sample of at least one of body liquid, tissue, and cells:

wherein expression of endometrial chorionic gonadotropin (eßhCG) in samples derived from non-pregnant women signals receptiveness of the endometrium for a fertilized egg;

wherein expression of endometrial chorionic gonadotropin (eßhCG) in samples derived from pregnant women signals an undisturbed pregnancy; and

wherein no expression of endometrial chorionic gonadotropin (eßhCG) in samples derived from non-pregnant women signals nonreceptiveness of endometrium for a fertilized egg and protection against pregnancy.

ARGUMENT

I. The missing Figure 1 is submitted.

To comply with the drawing requirement, Applicants hereby submit the missing Figure 1 along with this paper.

Applicants respectfully state that the Figure 1 submitted herewith is the same as the originally filed in the original International Application No. PCT/DE04/01210, and no new matter is added.

II. The typo of the sequence has been corrected.

In the Sequence Listing filed previously, the typo in "t?hCG" of SEQ ID NO. 2, identifier <223> was caused during the translation of the International Application. It has been corrected to become "tβhCG" as the originally filed. The correct version of Sequence Listing is submitted herewith, which is identical in material part to the Sequence Listing originally submitted in the PCT application. No new matter is introduced.

III. The objections to claims 22-24, 26-28 and 35 have been overcome.

The Examiner objected to claims 22-24, 26-28 and 35 for various alleged informalities. In response, Applicants have amended these claims to overcome the objections.

Specifically, the Examiner objected to claim 22 and suggested that the origin of the samples used in the method as claimed should be clarified. In response, Applicants have amended claim 22 by specifying the origins of the samples.

The Examiner also suggests to insert the SEQ ID NO.'s to various places in claims 22-24, 28, and 35. In response, the SEQ ID NO.s of the recited proteins have been added to claims 22-24 and 35, whereas claim 28 is amended so that it clearly relates to the methods of the previous claims and specifies the sample used in said method.

As suggested by the Examiner, claims 24 and 35 are amended by inserting the phrase "comprises using" before the phrase "at least one antibody that recognizes specifically human endometrial hCG."

Similarly, following the Examiner's suggestion, Applicants have also amended claims 22, 24, 26, and 27 by inserting the term "human" before the term "endometrial hCG."

Therefore, Applicants respectfully submit that all of the objections to the claims have been overcome.

IV. Rejection of claims 22-28 and 35 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The Examiner rejected claims 22-28 and 35 under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter witch Applicants regard as the invention.

Specifically, the Examiner rejected claim 22, alleging that it is not clear what constitutes "modification" due to lack of definition of the term in the specification. In response, claim 22 has been amended to direct to "[a] method for determining the receptivity of the endometrium and/or optimal implantation conditions in the uterus and/or the presence of an undisturbed pregnancy." Basis for this amendment can be found in the translation of the application as filed (WO-A2 2004/109292), on page 5, third paragraph.

The Examiner asserts that the term "eβhCG/ehCG" is indefinite because it is not clear whether one should determine the eβhCG subunit or ehCG. In response, claim 22 has been

amended by deleting the term "ehCG" to clarify that the method relates to the determination of the eβhCG subunit.

The Examiner asserts that in claim 22 the preamble is not consistent with the outcome of the recited method. Specifically, the preamble is "determining defined states or modifications in the *mucus membrane* of the uterus or in the epithelium of other organs" whereas the conclusion of the active steps recited in the claim 22 does not reflect the preamble. In response, the preamble of claim 22 has been amended to "[a] method for determining the receptivity of the endometrium and/or optimal implantation conditions in the uterus and/or the presence of an undisturbed pregnancy." As discussed above, support for this amendment is found in the original application filed.

The Examiner's clarity objection concerning the non-trophoblastic hCG (type I, β6 and β7) is not comprehensible to the applicant. The examiner states that the role of non-trophoblastic hCG is not clear in connection with the method. However, the aim of the determination of endometrial and non-trophoblastic hCG is unambiguously derivable from the specification as filed. The specification states that eβhCG is a variant of J36 and f37 hCG (*see* translation of WO-A2 2004/109292, page 6, first paragraph). The specification also discloses that the latter two are known non-trophoblastic hCG variants (*see* translation of WO-A2 2004/109292, page 6, last paragraph). It further states that it is the differentiation between trophoblastic hCG and endometrial/non-trophoblastic hCG variants is desired to, e.g., improve the diagnosis of an undisturbed pregnancy (*see* translation of WO-A2 2004/109292, page 7, third paragraph and page 14, second paragraph). However, to clarify that it is not in any case necessary to determine endometrial and non trophoblastic hCG variants the term "and" was exchanged by an "and/or" in claim 22.

The examiner further objected to the term "receptiveness" in claim 22 for lack of clarity. The examiner suggested specifying the term towards the receptiveness for embryo implantation. Applicants do not understand the objection as the claim unmistakably specifies the term as the "receptiveness of the endometrium for a fertilized egg." It is not clear why the wording shall be further "specified". By the method according to the invention, it is possible to diagnose the receptivity of the endometrium for a fertilized egg, *i.e.*, irrespective of whether fertilization was conducted *in vivo* or *in vitro*. Thus, for a person of ordinary skill in the art it is unambiguously

derivable from the wording that the term "receptiveness" in the context of the present invention relates to the capability of the uterus for the nidation of a fertilized egg or the implantation of an embryo. Thus, the term "receptiveness" in claim 22 is clear for a person of ordinary skill in the art.

In view of the amendment to the preamble of claim 22, the Examiner's objection to the term "other organs" in claim 22 has become moot.

The Examiner's objection to the clause "wherein a reduction of expression of endometrial chorionic gonadotropin (eßhCG/ehCG) in a pregnant woman with a healthy pregnancy signals a dysfunction of the endometrium or ..." has also been overcome by deletion of the clause from claim 22 as amended.

The Examiner further asked for clarification of the difference between the trophoblastic hCG (...tβhCG) and total βhCG measured in a method according to claim 23. By this step it is intended to determine the proportion of tβhCG and eβhCG (*see* translation of WO-A2 2004/019292, page 8, 4th paragraph). The specification clarifies that the proportion of tβhCG results from total hCG minus the measured eβhCG or the non-trophoblastic βhCG (*see* translation of WO-A2 2004/019292, page 8, 5th paragraph). Hence, the proportion of tβhCG and eβhCG can either be determined by direct measurement of tβhCG or eβhCG, respectively, or by determining the difference between the measured eβhCG level and the total hCG. Therefore, the wording of claim 23 has been specified as the determination of the proportion of eβhCG.

The dependency of claim 26 has been corrected so that the lack of antecedent basis for trophoblastic hCG or total βhCG or total hCG eliminated.

Claim 28 has been reworded and now relates to the methods of the previous claims and specifies the sample used in said method.

Finally, Applicants withdraw claim 36 from further consideration without prejudice to possible future prosecution; therefore, the objection to claim 36 is now moot.

Therefore, Applicants respectfully submit that all the rejections of the claims under 35 U.S.C. § 112, second paragraph, have been overcome.

V. Rejection of claims 22-28 and 35 under 35 U.S.C. § 112, first paragraph (enablement requirement), should be withdrawn.

The Examiner rejected claims 22-28 and 35 under 35 U.S.C. § 112, first paragraph, as

allegedly failing to comply with the enablement requirement.

The Examiner asked for "more tangible and concrete evidence" that the method according to the present invention is enabled for a person of ordinary skill in the art. Applicants hereby submit a document, Zimmermann et al., *Biol. Reprod.*, 2009, 80, 1053-1065 (*see* **Exhibit A**, hereinafter "Zimmermann et al."), as an Exhibit to show that the method according to the present invention is more than a mere hypothesis as insinuated by the examiner.

In the study underlying the document the concentration of βhCG and its proportion compared to total hCG in endometrial specimens was determined, *see* Zimmermann et al., Figure 2 and section "Evidence for the Presence-of hCG in Endometrial Tissue Homogenates and Intrauterine Secretion Material", spanning pages 1055 and 1056. The inventors have shown in said study that the proportion and the amount of βhCG in the endometrium is at highest levels during mid secretory and late secretory phase, respectively, whereas nearly undetectable during proliferative phase, see Zimmermann et al., Figure 2, and abstract, antepenultimate sentence: "Glandular endometrial hCG production is demonstrated immunoliistochemically, with an increase toward the late secretory phase vs. the early secretory phase of the normal secretory menstrual cycle."

Furthermore, the data presented in said document leads to the conclusion that the endometrial hCG is an important factor for the receptiveness of the endometrium and an undisturbed pregnancy, see Zimmermann et al., abstract, last sentence: "Endogenous endometrial hCG may be important for implantation and maintenance of pregnancy."

Even though it is formulated in the subjunctive, the conclusion is unambiguously derivable for a person of ordinary skill in the art from the data presented. Thus, Zimmermann *et al.* confirms the correlation between the concentration of endometrial βhCG and the receptiveness of the endometrium for fertilized eggs as disclosed in the present application. It follows that the method according to the invention is suited for the determination of the receptiveness of the endometrium for fertilized eggs.

"Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic.'" MPEP § 2164.02. "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of

experimentation." MPEP § 2164.02 (citing *In reBorkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)). "The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." MPEP § 2164.02.

In this case, in view of the extensive disclosure in the specification and the detailed diagnostic features of the method described in the claims, Applicants respectfully submit that the enablement requirement of 35 U.S.C. § 112, first paragraph, is satisfied and therefore request the withdrawal of this ground of rejection.

VI. Rejection of claim 36 under 35 U.S.C. § 102(b) has become moot.

The Examiner rejected claim 36 under 35 U.S.C. § 102(b) as allegedly being anticipated by Zimmermann et al. (*Molecular Human Reproduction*, 2003, Vol. 9, 81-89).

Applicants respectfully observe that this is the only rejection of claims in this Office Action based on prior art references. Without any indication of admitting to the merits of the rejection, solely to expedite the prosecution of the instant application, Applicants hereby cancel claim 36 without prejudice to possible future prosecution. Therefore, this ground of rejection has become moot.

CONCLUSION

Applicants believe that they have fully responded to the Examiner's concerns and that all the pending claims of this application are in condition for allowance; thus, an early notice to this effect is earnestly solicited. If the Examiner does not believe that such action can be taken at this time or if the Examiner feels that a telephone interview is necessary or desirable, Applicants welcome the Examiner to call the undersigned at 609-844-3020.

Please charge any deficiency and/or credit any overpayment to Deposit Account No. 50-1943. Thank you for your kind consideration in this matter.

Respectfully submitted,

Date: February 12, 2010

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